## Title

Association Of Non-Steroidal Anti-Inflammatory Drugs On Synovitis And The Progression Of Osteoarthritis: Data From The Osteoarthritis Initiative



## Authors

Luitjens, J
Gassert, F
Joseph, G
et al.

## Publication Date

2023-03-01

## DOI

10.1016/j.joca.2023.01.479

number encounters with a primary diagnosis of OA (Figure 1) but there was no statistical difference in the medications ordered from 2019 to 2020, 2019 to 2021, and the quarters between these years as well. After adjusting for Type I error, there was a significant decrease in medication refills from 2019 to 2020 (p-value 0.0031, adjusted p-value 0.0425) as well as from 2019 to 2021 (p-value <0.0001, adjusted p-value 0.003) (Figure 2), and there was a significant decrease in number of doses of analgesia from 2019 to 2020 and an increase in number of doses from 2019 to 2021 (p-value <0.0001, adjusted p-value 0.003) (Figure 3).

**Conclusions:** The COVID-19 pandemic has persistent impacts on the prescribing practices of analgesics for the treatment of OA. Our data suggests that since the COVID-19 pandemic, patients with OA were overall provided with more doses of analgesics and fewer refills. It is likely that barriers imposed by COVID-19 resulted in these changes in the way analgesics are provided for the treatment of OA.

## 459
## SCORE ASSESSMENT OF EFECTIVENESS OF KNEE OSTEOARTHRITIS TREATMENT WITH UNDENATURED COLLAGEN TYPE II

**D. Rekalov** [1], I. Golovach [2], I. Daniuk [3]. [1] *LLC Modern Clinic, Zaporizhzhia, Ukraine;* [2] *Feofaniya Clinical Hosp., Kiyv, Ukraine;* [3] *ZSMU, Zaporizhzhia, Ukraine*

**Purpose:** The autoimmune degradation of type II collagen plays the important role in the pathogenesis of OA. The search for a chondroprotective agent that would reduce the autoimmune mechanisms of collagen degradation is actual. The perspective agent is undenatured collagen type II (UC-II), oral administration of which contributes to the formation of immune tolerance and leads to reduce of T-killers attack of cartilage, decrease of proinflammation cytokines synthesis and increase of antiinflammation cytokines production. The purpose of the study was to assess the dynamics of Western Ontario McMaster Osteoarthritis Index (WOMAC) during UC-II administration in compare to glucosamine and chondroitin (G + Ch) combination in patients with Grade II knee OA.

**Methods:** 40 patients with Grade II knee OA were investigated. 20 patients were administrated the UC-II (40.0 mg cartilage collagen undenatured) during 180-day period, 20 patients took the combination of G + Ch during the same period. WOMAC index was used to evaluate the effectiveness and was completed before the start of therapy and after 180 days of treatment. Visual analog scale (VAS) from 0 to 10 was used for assessment the WOMAC subscale by patient.

Figure 1.

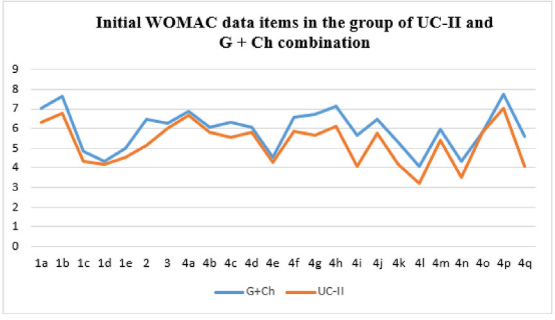
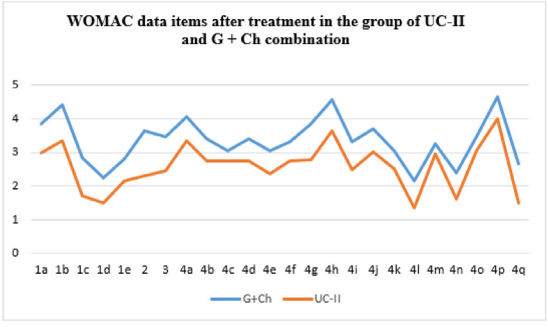



Figure 2.




**Results:** The initial and final results are presented in Figure 1 and Figure 2. The VAS score is set vertically, the WOMAC questions - horizontally. We detected that the therapy during 180-day period with UC-II and G + Ch combination significantly improved the most subscales of WOMAC index, which indicates to the positive therapeutic effect of both chondroprotective agents. Comparing both investigated groups demonstrated the better results according to decrease of WOMAC pain subscale in the group of UC-II: reduce of pain during walking (item 1a) by 28.76 % (2.99±0.37 to 3.85±0.35), decrease of stair climbing pain (item 1b) by 31.34 % (3.35±0.36 to 4.4±0.40), (item 1c) reduce of nocturnal pain by 67.65 % (1.70±0.41 to 2.85±0.51), reduce of rest pain (item1d) by 50.00 % (1.50±0.39 to 2.25±0.42) and weightbearing pain (item 1e) by 30.23 % (2.15±0.36 to 2.80±0.42) ($p < 0.05$). The administration of UC-II significantly decreased the morning stiffness (subscale 2) by 58.70 % in compared to the same WOMAC subscale in G + Ch treated group (2.30±0.4 to 3.65±0.33, $p < 0.05$). Similar dynamics was observed with the intensity of stiffness during the day (subscale 3). In this subscale UC-II demonstrated the statistically significant better result by 40.82 % (2.45±0.39 to 3.45±0.90, $p < 0.05$) compared to the combination of G + Ch. We detected the significant benefit in improving of the following indicators of functional mobility of knee joint in the group of UC-II: bending to floor (item 4e) by 29.79 % (2.35±0.46 to 3.05±0.49), walking on flat (item 4f) by 20.00 % (2.75±0.42 to 3.30±0.41), getting in/out of car (item 4g) by 37.99 % (2.79±0.39 to 3.85±0.39), going shopping (item 4h) by 24.66 % (3.65±0.46 to 4.55±0.45), lying in bed (item 4l) by 59.26 % (1.35±0.41 to 2.15±0.45), sitting (item 4n) by 49.07 % (1.61±0.44 to 2.40±0.41), light domestic duties (4q) by 77.85 % (1.49±0.34 to 2.65±0.47) ($p < 0.05$).

**Conclusions:** The therapy with Undenatured Type II Collagen during 180-day period in patients with Grade II knee OA demonstrates the significant benefit in reducing pain syndrome, joint stiffness and improving the most indicators of joint function in compare to Glucosamine and Chondroitin combination (according to WOMAC Index).

## 460
## ASSOCIATION OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON SYNOVITIS AND THE PROGRESSION OF OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

**J. Luitjens**, F. Gassert, G. Joseph, J. Lynch, M. Nevitt, N. Lane, C. McCulloch, T. Link. *UCSF, San Fransisco, CA*

**Purpose:** Osteoarthritis (OA) is characterized by bone and cartilage damage as well as synovial inflammation, which may be an important mediator for OA progression. With this model of an inflammatory contribution to the disease, synovitis could be an important therapeutic target. Anti-inflammatory drugs could potentially reduce synovitis through their influence on inflammation. There is limited information on how NSAID therapy impacts OA progression, and synovitis is a primary therapy target and therapeutic outcome. We investigated the association of NSAID use with synovitis, cartilage thickness and cartilage composition ($T_2$ relaxation time) in a longitudinal four-year observational study.

**Methods:** Participants from the Osteoarthritis Initiative (OAI) cohort with moderate to severe OA (Kellgren-Lawrence [K-L] grades 0-3) and sustained NSAID treatment for ≥1 year between baseline and 4-year follow-up were included and compared with non-NSAID treated participants (controls). Longitudinal analysis over 4 years was performed defining 3 cohorts: a NSAID sustained user group, a new user group, which started taking the NSAID between baseline and follow-up, and a control group without NSAID treatment (Figure 1). All participants underwent a 3T MRI of the knee at baseline and after 4 years. Images were semi-quantitatively graded for MR biomarkers of synovial inflammation (Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) score, MRI Osteoarthritis Knee Score (MOAKS) score, size, and signal intensity of infrapatellar fat pad (IFP), synovial proliferation score (SPS)). Cartilage thickness and $T_2$-relaxation time measurements served as non-invasive biomarkers for evaluating OA progression. The associations between the difference in baseline and change over 4 years and the three NSAID exposure groups (the new NSAID user group, the sustained NSAID user group, and controls) were investigated with linear regression models (including adjustments for sex, BMI, age, Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain scale, K/L grade).

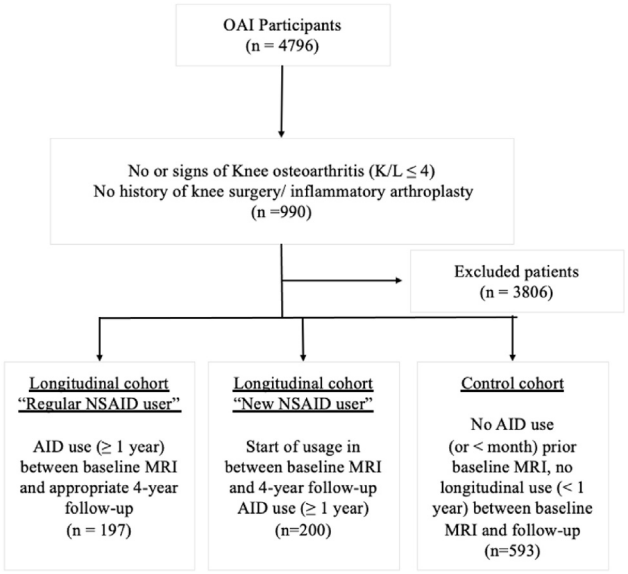



Figure 1- Flowchart depicting inclusion and exclusion criteria for NSAID user cohorts.

**Table 1.** Characteristics of analyzed groups at the baseline timepoint, for the cross-sectional analysis (baseline) and the longitudinal (baseline and 4-year follow-up) analysis.

| | | New NSAID user | Regular NSAID user | Controls | Total | p |
|---|---|---|---|---|---|---|
| | ***n*** | **200** | **197** | **593** | **990** | |
| **Age (years; mean, SD)** | | 60.7±9.5 | 60.9±8.9 | 59.1±8.8 | 59.9±9.1 | 0.01 |
| **BMI (kg/ m²; mean, SD)** | | 30.5±5 | 31.1±4.9 | 29.1±5.2 | 29.9±5.1 | <0.001 |
| **Sex** | ***Male (n, %)*** | 82, | 77, | 214, | 373 | 0.59 |
| | ***Female (n, %)*** | 118 | 120 | 379 | 617 | |
| **Kellgren/Lawrence** | ***Grade 0 (n, %)*** | 62 | 57 | 219 | 338 | 0.16 |
| | ***Grade 1 (n, %)*** | 38 | 42 | 117 | 197 | |
| | ***Grade 2 (n, %)*** | 66 | 67 | 190 | 323 | |
| | ***Grade 3 (n, %)*** | 32 | 29 | 61 | 122 | |
| **WOMAC[a]** | | 3.01±3.6 | 3.18±3.6 | 2.01±2.8 | 2.5±3.2 | <0.001 |
| **PASE[b]** | | 165.9±83.8 | 145.7±77.5 | 158.3±84.5 | 157.8±83.5 | 0.09 |

[a]The maximal possible WOMAC score is 10, comprises of five activities (surface walking, stair climbing, at night, sitting or lying, standing with each score ranging from 0 (no pain) to 2 (extreme pain). [b]
*BMI*, body mass index; *SD*, standard deviation. *WOMAC*, Western Ontario and McMaster Universities Osteoarthritis Index pain scale.

**Table 2.** Results for linear regression models for the association of findings (synovitis scores, cartilage thickness, T2 relaxation times) in NSAID users compared to controls

| | | Coef. | p | 95 % CI | |
|---|---|---|---|---|---|
| ***Change of ACLOAS*** | *New-NSAID user vs. C* | -0.003 | 0.96 | -0.13 | 0.12 |
| | *Regular NSAID user vs. C* | 0.06 | 0.35 | -0.07 | 0.19 |
| ***Change of MOAKS*** | *New-NSAID user vs. C* | 0.09 | 0.173 | -0.04 | 0.21 |
| | *Regular NSAID user vs. C* | 0.11 | 0.09 | -0.02 | 0.23 |
| ***Change of signal infrapatellar fat pad*** | *New-NSAID user vs. C* | -0.04 | 0.55 | -0.18 | 0.96 |
| | *Regular NSAID user vs. C* | 0.19 | **0.01** | 0.05 | 0.33 |
| ***Change of size infrapatellar fat pad*** | *New-NSAID user vs. C* | -0.10 | **0.01** | -0.17 | 0.03 |
| | *Regular NSAID user vs. C* | 0.01 | 0.74 | -0.06 | 0.09 |
| ***Change of Synovial proliferation score*** | *New-NSAID user vs. C* | 0.002 | 0.97 | -0.12 | 0.13 |
| | *Regular NSAID user vs. C* | 0.01 | 0.87 | -0.11 | 0.13 |
| ***Change of cartilage thickness in mm*** | | | | | |
| ***LT*** | *New-NSAID user vs. C* | -0.002 | 0.84 | -0.02 | 0.02 |
| | *Regular NSAID user vs. C* | 0.004 | 0.65 | -0.14 | 0.23 |
| ***MT*** | *New-NSAID user vs. C* | -0.01 | 0.28 | -0.03 | 0.01 |
| | *Regular NSAID user vs. C* | -0.02 | 0.82 | -0.02 | 0.02 |
| ***LF*** | *New-NSAID user vs. C* | -0.01 | 0.19 | -0.03 | 0.01 |
| | *Regular NSAID user vs. C* | -0.001 | 0.94 | -0.02 | 0.02 |
| ***MF*** | *New-NSAID user vs. C* | -0.01 | 0.36 | -0.40 | 0.1 |
| | *Regular NSAID user vs. C* | 0.003 | 0.81 | -0.02 | 0.03 |
| ***Change of T2 relaxation time in ms*** | | | | | |
| ***LT*** | *New-NSAID user vs. C* | 0.47 | **0.02** | 0.07 | 0.87 |
| | *Regular NSAID user vs. C* | 0.21 | 0.32 | -0.19 | 0.61 |
| ***MT*** | *New-NSAID user vs. C* | 0.40 | **0.03** | 0.05 | 0.75 |
| | *Regular NSAID user vs. C* | 0.35 | **0.05** | -0.004 | 0.71 |
| ***LF*** | *New-NSAID user vs. C* | 0.13 | 0.55 | -0.31 | 0.57 |
| | *Regular NSAID user vs. C* | 0.12 | 0.59 | -0.32 | 0.57 |
| ***MF*** | *New-NSAID user vs. C* | 0.02 | 0.92 | -0.38 | 0.43 |
| | *Regular NSAID user vs. C* | -0.05 | 0.82 | -0.46 | 0.36 |

ACLOAS = Anterior Cruciate Ligament OsteoArthritis Score; C = Control group; Coef. = Coefficient; CI = Confidence Interval; LF= Lateral Femur; LT = Lateral Tibia; MF = Medial femur; MOAKS = MRI; MT = Medial tibia Osteoarthritis Knee Score; p = p-value.

**Results:** A total of 990 participants were selected based on the inclusion and exclusion criteria. Participants' characteristics in the 3 cohorts are summarized in Table 1. Over 4 years participants with sustained NSAID usage showed signal intensity worsening of IFP Hoffa synovitis (beta coefficient [95% CI], p-value, 0.19, [0.05, 0.33], 0.01) without an effect on IFP size (0.01 [-0.06, 0.09], 0.74) (Table 2). In participants with new NSAID usage during the study, a decrease in IFP Hoffa synovitis size was found compared to the control group (-0.1 [0.05,0.33], 0.01) in the longitudinal analysis. A significant increase in $T_2$ relaxation time of the lateral (0.47 [0.07, 0.87], 0.02) and medial tibia (0.4 [0.05, 0.075], 0.03) was shown in the new NSAID users' group over time compared to controls). In addition, sustained NSAID users showed an increase in $T_2$ relaxation time in the medial tibia (0.4 [0.05, 0.75], 0.05) compared to controls. The cartilage thickness did not show a statistically significant change in NSAID users compared to controls over time.
**Conclusions:** In this observational study participants with sustained intake of NSAIDs over at least 1 year did not show a decrease in knee synovitis or any significant improvement in cartilage thickness or $T_2$ relaxation time compared to control participants. Furthermore, participants with sustained NSAID usage during the study demonstrated higher signal intensity in the IFP, indicating an association between NSAID usage and synovitis progression. These results suggest that anti-inflammatory drugs, at least in this study setting, had no beneficial effect. Additionally, NSAID users had significantly greater increase in T2 relaxation time values, suggesting higher progression of cartilage matrix degeneration without showing actual differences in cartilage thickness. Overall, our results suggest that NSAIDs used to improve clinical symptoms of OA had no beneficial effect on change in synovitis or cartilage thickness or composition over 4 years.

## 461
## EFFECTS OF ZHENWU SOUP COMBINED WITH SODIUM HYALURONATE INJECTION ON INFLAMMATORY FACTORS AND CHONDROCYTE METABOLISM IN RABBITS WITH KNEE OSTEOARTHRITIS

**z. yang** [1], W. Li [2]. [1] *Shaanxi Univ. of Traditional Chinese Med., Xianyang, China;* [2] *Ningqiang County Tianjin Hosp., Hanzhong, China*

Purpose: To observe the effects of Zhenwu soup combined with sodium hyaluronate injection on the expression of interleukin-6 (IL-6), interleukin-1 β (IL-1β), tumor necrosis factor-α (TNF-α) and MMP-13, TGF-β1, Col- ii in serum and synovial tissue of rabbit knee osteoarthritis (KOA).
Methods: Fifty healthy male New Zealand white rabbits, each with a body weight of 2.7±0.3Kg, were divided into 5 group: 10 normal group, 10 model group, 10 Zhenwu soup group (ZW), 10 sodium hyaluronate group (SH) by random number table method, with no significant difference (P>0.05). 10 patients were treated with Zhenwu soup and sodium hyaluronate (ZW+SH). Except for the normal group, the KOA model was made by surgical incision of the right knee ligament in the other four groups. Model group was injected with 0.3ml normal saline once a week for 6 weeks; ZW group injected 6 mL of warm Zhenwu soup into the stomach twice a day for 6 weeks; SH group was injected with 0.15ml sodium hyaluronate injection + 0.15ml normal saline once a week for 6 consecutive weeks; ZW+SH group was injected with gastric infusion of warm Zhenwu soup 6mL twice a day, sodium hyaluronate 0.15ml, injected once a week for 6 weeks. After 6 weeks, the rabbits were sacrificed, and the contents of IL-6, IL-1β and TNF-α in